REMARKS

Applicants thank the Examiner for reconsideration of the originally-proposed restriction groups, for combining original restriction Groups II and III, and for including claims 18-20 in original Group I of the parent application.

Applicants respectfully contend that all claims of presently elected restriction Group I, corresponding to claims 4-7, and 11-13 (and not only 4-6, and 11-13), should be pending, based on fact that applicants election of the instant Group I was made with the intent of prosecuting all encompassed claims of this Group.

Applicants contend that the inadvertent cancellation of claim 7 in applicants' Preliminary Amendment of 7/30/2000, paper #2, was unintended, being the inadvertent mistake of the prior attorney of record in this case who *prematurely* assumed, and stated in the Preliminary Amendment that claim 7 would be pending in the "parent application" (*see* Preliminary Amendment of 7/30/2000; paper #2). Applicants thus request that the Examiner kindly recognize the herein reinstated claim 7 as a proper pending claim of Examiners new Group I.

In any event, applicants respectfully request that claim 7 be reinstated, and if necessary given an appropriate new claim number (in this case 27).

Claims 1-3 and 8-10 (and inadvertently claim 7), as noted by the Examiner, were cancelled in a Preliminary Amendment (7/30/2000; paper #2) and claims 14-26 stand withdrawn by the Examiner pursuant to 37 C.F.R. 1.142 § (b), and are herein cancelled by applicants.

Claims 4-7, and 11-13 have been responsively amended herein to recite a requirement that the encoded polypeptides must comprise contiguous sequences of SEQ IN NO:1 and 2. Additionally, conforming functional language has been recited "wherein the polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}." Support for these amendments in the Specification has been cited, and discussed in view of the Examiner's rejections. Additionally, various amendments have been made in response to the Examiner's § 112 (second paragraph) rejections to further clarify the full scope of that which applicants regard as their invention.

No new matter has been added.

FORMALITIES

Applicants have responsively amended the specification by substitution of clean paragraphs to reflect proper use of trademarks (*see* Appendix A for marked up versions). Applicants appreciate the importance of Examiner's emphasis of this issue.

Applicants are preparing final formal drawings.

Rejections under 35 U.S.C. § 112 (Second Paragraph)

The Examiner rejected claims 4-6, and 11-13 under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner asserts that the recitation of "codes on expression for" in unclear (Office Action of 7/17/2001 at page 4, para 5).

Applicants have accordingly amended claims 4-7, and 11-13 to clarify the claimed subject matter. Specifically, the claims now recite "an isolated nucleic acid that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO...." The scope of the amended claims thus encompass *fragments* of consecutive amino acids of a defined length of the recited SEQ ID, *homologs or muteins* having consecutive amino acid regions of a defined length of the recited SEQ ID, *fusion proteins* containing all or a consecutive amino acid region of defined length of the recited SEQ ID. The recitation of functional language within the claims reasonably limits breadth to operative embodiments. Support for this amendment is found in Example 9 of the specification at pages 22-23, which discloses specific high-affinity binding of p68HER-2 (SEQ ID NO:2), and of its sub-domain ECDIIIa polypeptide fragment (SEQ ID NO:1) to solubilized and cell-bound p185HER-2 receptor. Support for functional fragments and fusion proteins is provided by the successful use of nickel agarose-immobilized "His-tagged" EDCIIIa for the binding studies.

Additionally, the Examiner asserts that the recitation of "extracellular domain ECD" in claims 4-6 is unclear (Office Action of 7/17/2001 at page 4, para 6).

Applicants have accordingly amended claims 4-6 to clarify the claimed subject matter. Specifically, these claims now recite "extracellular domain (ECD)."

The Examiner further asserts that the recitation of "10^8" in claims 4-6 is relative and unclear because it lacks "units," and that there is no "standard" provided by the specification (Office Action of 7/17/2001 at page 4, para 7).

Applicants respectfully traverse this basis of rejection, because the applicable units are widely recognized in the art as being M^{-1}, and because there is support for both the degree "standard" and "units" in the specification. While "a patent need not teach, and preferably omits, that which is known in the prior art" (MPEP Section 2164.01; *In re* Buchner, 929 F.2d 660, 661, 18 UPPQ2d 1331,1332 (Fed Cir. 1991)), applicants agree, that this is a legitimate point of clarification that should be addressed, and have accordingly amended claims 4-6 to recite "10^8 M^{-1}" in place of just "10^8." Support for this amendment is found in the specification at page 23, lines 29-30, and Figure 5C, which recite and show, respectively, that "the ECDIIIa peptide bound to intact 17-3-1 cells at **nM** concentrations." Thus the degree of binding is detectable in the *nanomolar* range (*i.e.*, corresponding to a binding constant equal to or greater than 10^8 M^{-1}). Additionally, the specification is replete with references to 'binding' and 'high-affinity binding' and recites the intent

to disclose novel high-affinity *binders* (*e.g.*,: the specification at page 1, line 30; at page 2 , line 26; at page 6, line 24 (in relation to the binding data Figure 5); at page 7, line 9 (in relation to the binding data of Figure 6)).

Therefore, applicants respectfully request withdrawalof this basis of rejection, based on applicants' responsive amendments, and because the term "10^8" was clearly intended to reflect a measure of binding affinity, and more specifically an affinity binding constant, widely recognized in the art as having units of M^{-1}.

Finally, the Examiner asserts that the recitation of the trademark/trade name "HERCEPTIN®" in claim 6 is inappropriate to designate goods, as opposed to the source of such goods.

Applicants have accordingly amended claim 6 to recite the generic terminology "the 4D5 humanized monoclonal antibody" in place of "HERCEPTIN®," as suggested by the Examiner.

Please note that applicants have also amended reinstated claim 7 to conform with all of the above-described responsive amendments.

In summary, applicants thank the Examiner for the thoughtful analysis and suggestions relating to the above issues, and respectfully request withdrawal of Examiner's § 112 second paragraph rejections with respect to amended claims 4-6, and 11-13 (and in pre-emptive fashion, to claim 7), based on applicants' responsive amendments. Claim 7 (amended), while not specifically reviewed by the Examiner, should be allowable if the nucleic acid of amended claims 4-6 are allowable.

Rejections under 35 U.S.C. § 112 (First Paragraph)

The Examiner rejected claims 4-6, and 11-13 under 35 U.S.C. § 112, second paragraph, as either lacking written description (claims 11-13), and/or enablement commensurate in scope to claim breadth. Applicants will address Examiner's rejections in the order asserted.

Claims 11-13 were rejected as containing insufficient description to adequately convey the claimed invention. The Examiner asserts the claims encompass a large nucleic acid "genus" encoding a polypeptide of variable sizes, but minimally comprising a fragment of SEQ ID NO:1, whereas the specification discloses only the structural features of two protein "species, the polypeptides of SEQ ID NO:1 and 2" (Office Action of 7/17/2001, at page 6, first full para), indicating that applicants were not in "possession of the broadly claimed genus.

Applicants respectfully traverse this written description rejection in view of applicants' following comments and limiting amendments of claims 11-13.

In addition to the requirement of the presence of the C terminal 79 amino acid residues of SEQ ID NO:2 in each of the encoded polypeptides, claims 11-13 have been amended to recite that the encoded 80-419 residues of SEQ ID NO:2 must be *contiguous*.

Furthermore, the claims have been amended to recite limiting functional language that the encoded "polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}."

Accordingly, the "broadly claimed genus" has been substantially narrowed to those polypeptides having a minimal *contiguous* 79 amino acid C terminal core sequence (SEQ ID NO:1), and which *retain the binding affinity of the full-length 419 amino acid p68HER-2 molecule.* Applicants respectfully contend that the amended claimed invention was well within applicants' possession at the time of filing.

Support for these amendments is found throughout the specification. Applicants invention is the first and only disclosure of a naturally occurring p185HER-2 binding protein and antagonist. Applicants have demonstrated and taught the binding properties of the full-length p68HER-2 and of the ECDIIIa sub-fragment (*see* Specification at page 22; Example 9, and Figure 5). In fact, the ECDIIIa sub-fragment tested in Example 9 was expressed from the pET30a vector (Novagen; see Specification at page 17, line 17) and thus represents a sizable *fusion* protein of ECDIIIa, comprising a heterologous amino terminal region of about 50 amino acids having: and poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site. Therefore, applicants have disclosed a minimal contiguous binding region, and have demonstrated its function in the context of much larger polypeptides (*i.e.*, p68HER-2 and a sizable diverse fusion protein).

Note that the recitation of "800" in originally submitted claim 11 was an inadvertent error, and has been amended herein to "80." Support for this amendment is found in the Specification at page 3, line 15, and in SEQ ID NO:2 itself, which contains only 419 amino acids.

Applicants respectfully request withdrawal of the Examiner's asserted § 112 first paragraph written description rejection with respect to amended claims 11-13.

Claims 4-6 and 11-13 were rejected by the Examiner under § 112 first paragraph as lacking *enablement*. The Examiner asserts, based on the listed *Wands* factors (Ex parte Forman), that the specification does not reasonably enable claims that are broadly drawn to isolated polynucleotides encoding polypeptides comprising "about 50-79 amino acids taken from SEQ ID NO:1, or from about 80-419, or 800-419 or about 350-419 amino acids taken from SEQ ID NO:2," where the "claims do not require that these amino acids be contiguous." (Office Action of 7/17/2001 at page 7, second full para).

Applicants respectfully traverse this § 112 first paragraph enablement rejection, based on applicants following comments and limiting amendments of claims 4-6 and 11-13.

As discussed above, applicants have amended claims 4-6 and 11-13 to recite that the encoded residues of SEQ ID NO:1 or 2 must be *contiguous*.

Furthermore, the claims have been amended to recite limiting functional language that the encoded "polypeptide binds to the extracellular domain (ECD) of HER-2 with an affinity binding constant of at least 10^8 M^{-1}."

Additionally, applicants respectfully respond to the Examiners assertion that "the specification provides no objective evidence that any other isolated polypeptides would function as ECDIIIa and p68HER-2 do (Office Action of 7/17/2001, at page 7, last para). In fact, as discussed above, the ECDIIIa sub-fragment tested in applicants' Example 9 was expressed from the pET30a vector (Novagen; *see* Specification at page 17, line 17) and thus represents a sizable *fusion* protein of ECDIIIa, comprising a heterologous amino terminal region of about 50 amino acids having: and poly-histidine tag; a thrombin cleavage site; an S-tag region; and an enterokinase site. Therefore, applicants have disclosed a minimal contiguous binding region, and have demonstrated its function in the context of much larger polypeptides (*i.e.*, p68HER-2 and a sizable diverse fusion protein).

Applicants thank the Examiner for the discussion of Bowie et al. (Science, 1990, 247:1306-1310) and Bork (Genome Research, 2000, 10:398-400), and recognize the predictability issues associated with *substitutions* within functional coding regions of proteins, and with comparative sequence analysis.

However, applicants' claims 4-7, and 11-13 have been amended to recite that the functional encoded residues of SEQ ID NO:1 or 2 must be *contiguous*, and thus not substituted. Amended claims 11-13 require that the contiguous 79 amino acid C-terminal region of SEQ ID NO:2 be present and unsubstituted. Thus, the issues articulated by Bowie and Bork, while relevant, have been addressed by the requirement of contiguous amino acids of SEQ ID NO:1 or 2, and the functional language of the amended claims.

Finally, claim 6 was rejected by the Examiner under § 112 first paragraph as lacking *enablement*. The Examiner asserts there is no requirement that the 50-79, or 69-79 amino acids taken from SEQ ID NO:1 be contiguous, and furthermore that the Specification provides "no guidance or objective evidence" that any such encoded polypeptides, including ECDIIIa or p68HER-2, would "bind to a site other than that bound by the HERCEPTIN antibody." Additionally, the Examiner points out that the binding site of the HERCEPTIN antibody is not defined (Office Action of 7/17/2001 at page 11, second and third full paras).

Applicants respectfully traverse this § 112 first paragraph enablement rejection, based on applicants following comments.

Applicants' specification at page 12, line17-19, recites that "the site of such binding is different and unaffected by the site of binding of a marketed humanized monoclonal antibody (Herceptin®)." Applicants' evidence in this regard is represented by the results of applicants'

Example 10 at pages23-24 of the Specification. Example 10 shows that pECDIIIa and p68HER-2 had no effect on tyrosine phosphorylation of p185HER-2. This is in marked contrast to the art-recognized effects of the HERCEPTIN® humanized monoclonal antibody at the time of filing of the parent application. There is thus a strong likelihood that the binding site of pECDIIIa and p68HER-2 is, at least in part distinct, from that of HERCEPTIN® humanized monoclonal antibody.

Applicants have, in view of the Examiner's comments, amended claim 6 to recite that "the polypeptide binds to a site on the extracellular domain (ECD) of HER-2 that is, at least in part, distinct from the site of binding of the 4D5 humanized monoclonal antibody (HERCEPTIN®)."

Therefore, applicants respectfully request withdrawal of the Examiners § 112 first paragraph enablement rejection with respect to amended claim 6.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request allowance of the "clean" claim set provided herein above. The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

No new matter has been added. Entry of the Amendment is respectfully requested.

Respectfully submitted,

Davis Wright Tremaine LLP

Barry L. Davison
Attorney for Applicant
Registration No. 47,309

Davis Wright Tremaine LLP
2600 Century Square
1501 Fourth Avenue
Seattle, Washington 98101-1688
Telephone: 206-628-7621
Facsimile: 206-628-7699